Hemolytic Anemia Due to Progressive Enlargement of Silastic Ball Component of Aortic Prosthesis

By Mario C. Garcia, M.D., Albert M. Clarysse, M.D., Carl S. Alexander, M.D., Ph.D., Yoshio Sako, M.D., Ph.D., and William R. Swaim, M.D.

SUMMARY

The patient described developed hemolytic anemia following insertion of a Starr-Edwards aortic valve prosthesis. No diastolic murmur was heard and no insufficiency was detected. The hemolytic anemia was progressively more severe and uncompensated despite various medical measures.

The anemia was characterized by fragmented erythrocytes in the peripheral blood, reticulocytosis, elevation of plasma heme pigments augmented by exercise, increased fecal urobilinogen, and iron loss in the urine. Studies of chromium-51-tagged erythrocytes indicated an extravascular mechanism of hemolysis.

At reoperation the ball component of the prosthesis was found to be enlarged and obstructing blood flow. Chemical analysis of the ball showed significant cholesterol and lipid deposits. The hemolysis disappeared after the prosthesis was replaced with a homograft valve. Ferrokinetic studies showed rapid plasma clearance and incorporation into circulating erythrocytes. Triglycerides were elevated during the period of hemolysis. Red cell membrane lipids were normal.

Additional Indexing Words:
Ferrokinetic studies of erythrocytes
Chromium-tagged erythrocyte studies
Lipids in erythrocytic membrane

Triglycerides
Cholesterol

The development of artificial valves has played a major role in correcting the hemodynamic complications of diseased aortic, mitral, and tricuspid valves. Although most patients have an improvement in their cardiac function, some develop hemolytic anemia which is clinically distinct from the post-perfusion hemolysis described by Kreeel and associates. Hemolytic anemias have been described in association with diseased aortic and mitral valves, as well as aortic and mitral valve prostheses, and without insufficiency.

This paper describes a patient with a Starr-Edwards aortic valve in whom progressively more severe hemolytic anemia developed in the absence of aortic valve insufficiency, over a 2-year period after surgery. Brachial artery pressure tracings obtained near the end of the second year were suggestive of development of stenosis. The hemolytic anemia could not be controlled by medical management. The prosthesis was therefore replaced by a homograft aortic valve. The silastic* ball component of the

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* Dow-Corning Corporation, Midland, Michigan.
Starr-Edwards valve was found to be enlarged, roughened, covered with lipids, and obstructing blood flow through the valve. This enlargement resulted in restriction of free movement of the ball within its cage.

**Report of Case**

W. G., a 40-year-old white farmer, gave a history of migratory joint pains at age 12 years and was found to have a heart murmur when he entered the Armed Forces in 1940. After discharge from the Army, he was asymptomatic except for an episode of pericarditis of unknown etiology in 1956. In April 1962, he was hospitalized at the Minneapolis Veterans Administration Hospital for congestive heart failure. His blood pressure was 120/99 mm Hg, a thrill was palpable at the left second intercostal space, and a grade IV/VI systolic murmur was heard in the same area with transmission into the neck and down to the apical area of the heart. Laboratory studies showed the following values: hemoglobin of 15.6 g%, hematocrit of 44%, and serum cholesterol of 328 mg%, normal glucose tolerance, normal blood urea nitrogen, and a negative rheumatoid latex fixation test. Other findings included left ventricular hypertrophy by chest roentgenography and electrocardiogram, aortic valve calcification by cinefluoroscopy, and aortic stenosis without regurgitation by left ventriculography. The patient responded well to salt restriction and digitalization. Two years later, in April 1964, he was readmitted because of orthopnea, paroxysmal nocturnal dyspnea, and lightheadedness. At this time the aortic valve was replaced with an 11-A Starr-Edwards prosthesis. In the 2 weeks following surgery, his hemoglobin level, which was 15 g% in the preoperative and immediate postoperative period, gradually fell to

### Table 1

**Hematological Studies**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Values after Starr-Edwards prosthesis</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fragmented red cells in peripheral blood smear (%)</td>
<td>8.5 - 8.8</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>2. Hemosiderinuria (Prussian blue)</td>
<td>Persistently (+)</td>
<td>(-)</td>
</tr>
<tr>
<td>3. Plasma heme pigments (mg%)</td>
<td>41 - 90</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>4. Fecal urobilinogen (mg%/24 hr)</td>
<td>Up to 1,030</td>
<td>20 - 280</td>
</tr>
<tr>
<td>5. Coombs' test: Direct</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Indirect</td>
<td>(+) (Kjell)</td>
<td>(-)</td>
</tr>
<tr>
<td>6. Autohemolysis (% in 48 hr)</td>
<td>2.3, control 1.6</td>
<td>0.4 to 4.5</td>
</tr>
<tr>
<td>7. Donath-Landsteiner</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>8. Sugar hemolysis</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>9. Acid hemolysis</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>10. Serum folic acid level (mg/ml)</td>
<td>9.6</td>
<td>6.4 - 25</td>
</tr>
<tr>
<td>11. Serum B12 level (total) (γγ/ml)</td>
<td>290</td>
<td>155-583</td>
</tr>
<tr>
<td>12. Serum Fe (µg%) before iron therapy; After or during iron therapy</td>
<td>45, 48, 73, 63</td>
<td>55 to 175</td>
</tr>
<tr>
<td>13. Osmotic fragility</td>
<td>Normal</td>
<td>No hemolysis in 0.95 to 0.51% NaCl</td>
</tr>
<tr>
<td>14. Hemoglobin electrophoresis (acrylamide gel)</td>
<td>Normal adult</td>
<td>—</td>
</tr>
<tr>
<td>15. ⁵¹Cr red cell survival T/2 (days); Segregation: spleen/liver</td>
<td>Pt. 9, donor 6</td>
<td>24 - 31</td>
</tr>
<tr>
<td>16. ⁵⁹Fe plasma clearance, T/2 (min); Red cell ⁵⁹Fe incorporation</td>
<td>1.2</td>
<td>0.8 - 1.2</td>
</tr>
<tr>
<td>17. Bone marrow, 1966</td>
<td>32, 27.5</td>
<td>60 - 90</td>
</tr>
<tr>
<td>Bone marrow, 1967</td>
<td>80% in 7 days</td>
<td>90% in 8-10 days</td>
</tr>
<tr>
<td>18. Effect of physical activity on plasma hemoglobin level (total heme pigments) (mg%)</td>
<td>66% in 4 days</td>
<td>90% in 8-10 days</td>
</tr>
</tbody>
</table>

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11.1 g%. Three plasma heme pigment determinations yielded 41, 51, and 85 mg%, with the normal range being less than 5 mg%.

One year later, in May 1965, the cardiac output was 5.5 L/min, cardiac index was 2.8 L/min /m², brachial artery pressure, 102/75 mm Hg, brachial artery peak velocity, 525 mm/sec, and brachial artery rise time of 0.18 sec was corrected for rate to 0.20 sec. These data indicate that aortic outflow was partially obstructed. The hemoglobin was 10.6 g%, reticulocyte count was 6.8%, and marked poikilocytosis of the erythrocytes was observed in the blood smear. The serum bilirubin was 1.0 mg% total with 0.1 mg% direct, and the serum iron was 21 μg% with a total iron-binding capacity of 289 μg%. The serum cholesterol was 160 mg%. Multiple guaiac tests of stools were negative, and tests of urine for hemosiderin were repeatedly positive.

Special hematological studies were done because of the progressive anemia, the results are listed in table 1. These data indicate that the anemia was hemolytic in nature and was characterized by the presence of numerous fragmented erythrocytes (schistocytes) in the blood smear (fig. 1), reticulocytosis, elevation of plasma heme pigments augmented by exercise, increased fecal urobilinogen, decreased serum iron, persistently positive hemosiderinuria, and a striking normoblastic hyperplasia of the bone marrow. Studies of erythrocytes tagged with radiocromium (⁵¹Cr) (fig. 2) showed a shortened survival

Figure 1
Schistocytes, peripheral blood smear.

Figure 2
Survival of Chromium-5¹-tagged erythrocytes.
time using the patient's own cells as well as with normal compatible donor cells. These findings indicate that an extra corpuscular mechanism was largely responsible for the hemolysis. Studies for an antibody-related mechanism were negative. Screening tests for intrinsic erythrocyte abnormalities were either negative or within normal limits. Quantitative analysis (table 2) of lipids in the erythrocytic membrane showed that they were within normal limits. Plasma lipids studied at the same time revealed a triglyceride level of 420 mg\% (normal, 100 to 160 mg\%). Cholesterol and phospholipids were within normal limits. Ferrokinetic studies (fig. 3) revealed a rapid plasma clearance of intravenously injected, radioisotope-labeled iron. External monitoring (fig. 4) showed a rapid increase in counts over the bone marrow declining over the next 3 days to a plateau. With the decline in marrow radioactivity there was a simultaneous increase and plateau in the liver and spleen radioactivity. The peak incorporation of $^{59}\text{Fe}$ into circulating erythrocytes was reached by the fourth day and was followed by a progressive decrease for the next 5 days of study. During this 5-day period the radioactivity of both the liver and spleen increased. Thus, iron incorporation into the erythrocytes was rapid and reached a peak value earlier than the normal expected peak between 7 to 10 days.$^{18,19}$ The decrease in the $^{59}\text{Fe}$-tagged erythrocyte population coupled with the increased spleen and liver counts indicates that these organs were participating in the clearance of damaged erythrocytes. Ordinarily the spleen is the prime remover of damaged erythrocytes, but when cell damage is severe, the liver participates as well.$^{20}$

Figure 3 depicts the clinical course of this patient and the various measures attempted to stabilize the hemoglobin level. Following surgery in 1964, there was a progressive decrease in hemoglobin with a corresponding brisk reticulocytosis. Transfusions of packed erythrocytes given to reduce the high output state associated with the anemia, were only partially successful in ameliorating the brisk hemolysis. Periods of reticuloecytopenia regularly followed blood transfusion. Oral iron therapy, given to cover the urinary iron losses, resulted in a return of iron

### Table 2

**Erythrocyte Membrane Lipids**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lipid weight</td>
<td>$5.58 \times 10^{-10} \text{mg/RBC}$</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>28.1% by weight</td>
</tr>
<tr>
<td>% of phospholipids</td>
<td></td>
</tr>
<tr>
<td>Phosphatidyl ethanolamine</td>
<td>26.1</td>
</tr>
<tr>
<td>Phosphatidyl choline</td>
<td>30.9</td>
</tr>
<tr>
<td>Phosphatidyl serine</td>
<td>14.7</td>
</tr>
<tr>
<td>Sphingomyelin</td>
<td>25.1</td>
</tr>
<tr>
<td>Phosphatidic acid</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Obtained during period of hemolysis associated with the Starr-Edwards valve.
to the bone marrow. Nevertheless, this iron therapy did not result in compensation of the anemia. Folic acid, prednisone, and pyridoxine were of no obvious benefit. Testosterone was not successful in stimulating erythropoiesis in the already hyperplastic bone marrow. An accentuation of hemolysis associated with physical activity was documented by an increase in the level of plasma heme pigments. The hemolytic anemia was progressively severe and was only partially responsive to conservative measures. The patient’s activities were increasingly restricted because of the brisk hemolysis.

In February 1967, physical findings included marked pallor and a grade II/VI systolic murmur at the base of the heart. The liver and spleen were not enlarged by physical examination or roentgenography. Brachial artery pressure tracings suggested moderate aortic valvular stenosis. There was no valvular insufficiency by aortography (fig. 6). A homograft aortic valve was inserted in June 1967 by Dr. John W. Kirklin in Birmingham, Alabama. At operation, the Starr-Edwards ball was found to be “extremely enlarged and almost

Figure 5
Clinical course.

Figure 6
Aortogram.
immobile within the cage” creating an outflow obstruction (fig. 7). The postoperative course was uneventful. A grade II/VI systolic murmur, heard at the base has persisted but is considered to have no hemodynamic significance.21 The patient was discharged without any medications.

Examination of the ball by Edwards Laboratories, Inc., manufacturer of the valve, revealed that it was yellow-white with several deep strut marks and shallow abrasions (fig. 8). The ball weighed 4.066 g, an increase of 20.2% over the original weight of 3.384 g. There was a 3.7 to 8.7% increase in the overall dimensions of the ball. The degree of hardness was unchanged. Analysis of a chloroform methanol extract of the ball indicated that there was approximately 54 mg of cholesterol (total) on the ball. Thin layer chromatography of the cholesterol assay mixture revealed cholesterol and cholesterol esters, triglycerides, free fatty acids, and phospholipids (no quantitative data). Silicic acid column chromatography and thin layer chromatography of the residue of the chloroform-methanol extraction revealed these same materials plus cardiolipin. Streaking was noted in the area of lecithin and lyssolecithin, but they were not positively identified.

Examination of the patient 2 months after insertion of the homograft showed he had a systolic murmur at the base transmitted to the neck and apex and a faint early diastolic murmur in the same area. The hemoglobin concentration was 14 g%, reticulocyte count was 0.9%, and red cell fragments had disappeared from the peripheral blood. The serum bilirubin was 0.3 mg% total and 0.1 mg% direct. Serum iron was 55 µg% with a total iron-binding capacity of 168 µg%. The concentration of serum glutamic-oxalacetic transaminase was 48 units and that of cholesterol was 176 mg%. Urine tests for hemosiderin were positive. This finding was interpreted as spillage of residual renal tubular iron deposits since serum haptoglobin levels were normal. The urine hemosiderin tests remained positive for 9 months following insertion of the homograft valve. The patient’s 51Cr-tagged erythrocyte survival was normal with a half-life of 24 days.

Figure 7

Starr-Edwards prosthesis. (Top) New prosthesis. (Bottom) Patient’s prosthesis.

Figure 8

Ball component of patient’s prosthesis.
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Discussion

The patient described developed severe hemolytic anemia as a result of enlargement of the silastic ball component of a Starr-Edwards valve. The development of stenosis was suspected and documented prior to reoperation. The patient's activities were increasingly limited because of the severity and progressive nature of the hemolytic anemia. Because of this the Starr-Edwards prosthesis was replaced by a homograft valve.

Cases of enlargement of the ball have been reported in the literature, but the nature of the enlargement has not been described. These have been associated with cardiac decompensation due to severe outflow obstruction.\textsuperscript{12, 13, 18–26} The anemia associated with the enlarged ball has not previously been characterized. The anemia in this patient was the result of extracorporeal mechanisms of erythrocyte destruction related to an enlarged, roughened ball which obstructed outflow across the Starr-Edwards prosthesis.

The mechanism of erythrocyte destruction is unclear. Patients with prosthetic valves or patch prostheses generally have a mild compensated hemolytic anemia unless the valves are grossly malfunctioning. Several theories have been advanced to explain the mechanism of hemolysis, including: trapping of cells between the rigid case and ball,\textsuperscript{27} trauma to the red cells as they collide with Teflon,\textsuperscript{28, 29} autoimmunity,\textsuperscript{30} cell collision with Dacron cloth valves,\textsuperscript{31} and turbulent blood flow.\textsuperscript{32, 33} Turbulent blood flow has been present in all cases of severe hemolysis associated with prosthetic valves. Regurgitation was present in most. In the present case, despite an absence of regurgitation, severe hemolytic anemia was observed in association with a progressive increase in the size of the ball component of the valve. Since this created an obstruction to outflow, it is reasonable to expect an increase in turbulence. Also, the roughened surface of the ball may have accentuated the turbulence, or perhaps contributed to the destruction of erythrocytes striking its surface. The presence of numerous fragmented erythrocytes in the peripheral smear, the elevated plasma heme pigment levels, and the persistent hemosiderinuria clearly pointed to intravascular hemolysis. Chemically induced hemolysis was unlikely since the materials used in the Starr-Edwards valve are inert substances and incubation of red cells with these materials does not result in hemolysis.\textsuperscript{32} Many intrinsic and some extrinsic erythrocytic abnormalities leading to hemolysis\textsuperscript{29} were searched for in this patient but were not detected. The slightly positive indirect Coombs' test was due to an anti-Kjell antibody and was most probably related to multiple transfusions. Ferrokinetic studies revealed rapid plasma clearance and rapid reappearance of iron in circulating erythrocytes. The percentage of iron-59 incorporated into erythrocytes was less than expected. This was falsely low because of the brisk random hemolysis of tagged and untagged circulating erythrocytes. The early\textsuperscript{50}Fe peak reappearance in circulating erythrocytes, plus the normoblastic hyperplasia of the marrow and the reticulocytosis indicated that the marrow was responding, but was not fully effective in compensating for the intense destruction of erythrocytes. The anemia failed to respond to a variety of drugs, singly or in combination. Exercise intensified the anemia. In contrast, may patients with hemolytic anemia, associated with prosthetic valves, have been compensated by administration of iron\textsuperscript{6, 22, 34, 35} or by iron and a reduction in physical activity.\textsuperscript{56}

The mechanism of ball enlargement is unclear but appears to be related, in part, to cholesterol and lipid deposition on the ball. It is of interest that our patient's cholesterol level prior to his initial valve replacement was 328 mg%. It would be important to know whether hypercholesterolemia or hyperlipidemia is an additional hazard to patients with the Starr-Edwards type of prosthesis using a silastic ball.

Several months after insertion of a homograft valve, the patient is active and has normal blood parameters except for a cholesterol level of 284 mg%. His cardiac function had improved to the point that he was able
to participate in a 9-day deer hunting expedition.

Barratt-Boyes, Kirklin, Nelson, and their associates have reported that a homograft valve has little or no obstruction to flow and no need for chronic anticoagulation.21, 37, 38 Our studies of $^{51}$Cr-tagged erythrocytes with normal serum haptoglobin levels indicate there is minimal or no destruction of erythrocytes with the homograft valve. Only the matter of durability is still in doubt.

Acknowledgments

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